CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 074593

Trade Name Etomidate Injectable 2mg/ml
10 and 20ml vials

Generic Name Etomidate Injectable

Sponsor Bedford Laboratories

ANDA 74-593

Bedford Laboratories
Division of Ben Venue Laboratories, Inc.
Attention: Robert V. Kasubick, Ph.D.
300 Northfield Road
Bedford, OH 44146

Dear Sir:

This is in reference to your abbreviated new drug application dated December 12, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Etomidate Injection, 2 mg/mL; 10 and 20 mL vials.

Reference is also made to your amendments dated January 23, September 26, October 22 and 29, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Etomidate Injection 2 mg/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Amidate of Abbott Laboratories Hospital Products Division.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

11.1.96

Roger L. Williams, M.D.
Deputy Center Director
for Pharmaceutical Science
Center for Drug Evaluation and Research

ANDA No. 74-593, Etomidate Injection 2 mg/mL, 10 & 20 cc vials

ADDENDUM TO CHEMISTRY REVIEW NO. 3

The method validation evaluation performed by the field laboratory recommended that the subject ANDA be withheld from approval due to a problem found with the etomidate raw materials identified as a sample and a reference standard. Both samples came from the same lot of raw material (i.e., lot no. K30800). The chemist reported that one of the samples appeared as a free-flowing granular material with a particle size of 1 to 4 mm and that the other sample was a clumpy powder with a particle size of 0.2 mm or less, therefore, failing the appearance analysis which raises a sample integrity issue.

The IR spectra acquired by our lab for these samples **show no differences at all in the physical character of these samples**. Lets be reminded that small crystals tend to adhere to larger crystal under low RH conditions, therefore, making larger individual crystals. Also, the crystallization step in the synthetic process may produce a wide particle size distribution if this step is repeated until little product is recovered and the final drug substance is grounded with a mortar and pestle before packaging. Only the drug substance is synthesized per batch.

On October 22, 1996, a tele-communication with the firm was initiated to resolve the above mentioned problem with the appearance analysis for the NDS reported by Kenneth Scholz, Field Chemist, Cincinnati District Office. The firm accepted and committed to supplement the ANDA with the results of the study proposed by OGD and accepted by the District Lab to resolve this appearance description issue. See telecom memo dated 10/22/96, for a breakdown of the analysis to be performed for the subject study.

The District Lab was contacted and informed of the commitment obtained from the firm to supplement the ANDA and the type of tests that were to be performed including a definite period for the completion of the study. Mr. Kenneth Scholz agreed with the proposal. The District Lab sent a letter dated October 28, 1996, stating that "the important matter is a study to resolve the raw material appearance problem without holding up the application."

The subject drug substance has no compendial monograph. The appearance description from three different sources are as follows: 1) crystals; 2) white or yellow crystal or amorphous; and 3 fine white powders. Because of the inconsistencies between these three reputable sources and the lack of a compendial monograph to address the appearance definition of etomidate raw material, the possibility of a sample or data integrity problem is a mere theory. Also, let's consider that the inspection reported that s was in compliance with cGMPs as of 4/25/96. Recommend approval of the subject application.

Edwin Ramos, Chemist Reviewer
10/29/96

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-593

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories
Division of Ben Venue Laboratories, Inc.
Attention: Robert V. Kasubick, Ph.D.
300 Northfield Road
Bedford, OH 44146

4. LEGAL BASIS FOR SUBMISSION
The applicant includes a basis for ANDA Submission statement on page 04. Also included is a copy of the Prescription Drug Product List from FDA's Approved Drug Products for the "listed drug". To the best of the firm's knowledge there is no patent in effect for Abbott Laboratories Amidate. The conditions of use, the active ingredient, the route of administration, dosage form and strength of the proposed drug product are the same as the approved listed drug (Amidate).

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Etomidate Injection

7. NONPROPRIETARY NAME
Amidate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Date of Application 12/19/94
New Correspondence 12/29/94
ANDA Acknowledgement Letter 1/23/95
FDA Deficiency Letter 4/26/95
Amendment Response 6/20/95
FDA Deficiency Letter 12/4/95
Amendment Response 1/23/96
Telecom 10/22/96
Telecom Amendment 10/22/96

10. PHARMACOLOGICAL CATEGORY
Anesthetic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Injection IV

14. POTENCY
2 mg/mL, 10 & 20 mL vial

15. CHEMICAL NAME AND STRUCTURE
R-(+)-ethyl-1-(1-phenylethyl)-1H-imidazole-5-carboxylate

16. RECORDS AND REPORTS
N/A

17. COMMENTS
All deficiencies have been addressed satisfactorily.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is approvable.

19. REVIEWER:
Karen A. Bernard, Ph.D.

DATE COMPLETED:
3/28/96

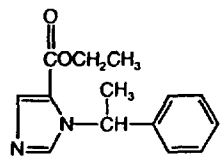
ETOMIDATE INJECTION

DESCRIPTION

Etomidate Injection is a sterile, nonpyrogenic solution. Each milliliter contains etomidate, 2 mg, propylene glycol 35% v/v.

It is intended for the induction of general anesthesia by intravenous injection.

The drug etomidate is chemically identified as (+)-Ethyl 1-(α-methylbenzyl)imidazole-5-carboxylate and has the following structural formula:



Molecular Formula: $C_{14}H_{16}N_2O_2$ Molecular Weight: 244.29

CLINICAL PHARMACOLOGY

Etomidate is a hypnotic drug without analgesic activity. Intravenous injection of etomidate produces hypnosis characterized by a rapid onset of action, usually within one minute. Duration of hypnosis is dose dependent but relatively brief, usually three to five minutes when an average dose of 0.3 mg/kg is employed. Immediate recovery from anesthesia (as assessed by awakening time, time needed to follow simple commands and time to perform simple tests after anesthesia as well as they were performed before anesthesia), based upon data derived from short operative procedures where intravenous etomidate was used for both induction and maintenance of anesthesia, is about as rapid as, or slightly faster than, immediate recovery after similar use of thiopental. These same data revealed that the immediate recovery period will usually be shortened in adult patients by the intravenous administration of approximately 0.1 mg of intravenous fentanyl, one or two minutes before induction of anesthesia, probably because less etomidate is generally required under these circumstances (consult the package insert for fentanyl before using).

The most characteristic effect of intravenous etomidate on the respiratory system is a slight elevation in arterial carbon dioxide tension ($PaCO_2$). See also **ADVERSE REACTIONS.**

Reduced cortisol plasma levels have been reported with induction doses of 0.3 mg/kg etomidate. These persist for approximately 6 to 8 hours and appear to be unresponsive to ACTH administration.

The intravenous administration of up to 0.6 mg/kg of etomidate to patients with severe cardiovascular disease has little or no effect on myocardial metabolism, cardiac output, peripheral circulation or pulmonary circulation. The hemodynamic effects of etomidate have in most cases been qualitatively similar to those of thiopental sodium, except that the heart rate tended to increase by a moderate amount following administration of thiopental under conditions where there was little or no change in heart rate following administration of etomidate. There are insufficient data concerning use of etomidate in patients with recent severe trauma or hypovolemia to predict cardiovascular response under such circumstances.

Clinical experience and special studies to date suggest that standard doses of intravenous etomidate ordinarily neither elevate plasma histamine nor cause signs of histamine release.

Limited clinical experience, as well as animal studies, suggests that inadvertent intra-arterial injection of etomidate, unlike thiobarbiturates, will not usually be followed by necrosis of tissue distal to the injection site. Intra-arterial injection of etomidate is, however, not recommended.

Etomidate induction is associated with a transient 20-30% decrease in cerebral blood flow. This reduction in blood flow appears to be uniform in the absence of intracranial space occupying lesions. As with other intravenous induction agents, reduction in cerebral oxygen utilization is roughly proportional to the reduction in cerebral blood flow. In patients with and without intracranial space occupying lesions, etomidate induction is usually followed by a moderate lowering of intracranial pressure, lasting several minutes. All of these studies provided for avoidance of hypercapnia. Information concerning regional cerebral perfusion in patients with intracranial space occupying lesions is too limited to permit definitive conclusions.

Preliminary data suggests that etomidate will usually lower intraocular pressure moderately.

Etomidate is rapidly metabolized in the liver. Minimal hypnotic plasma levels of unchanged drug are equal to or higher than 0.23 µg/mL; they decrease rapidly up to 30 minutes following injection and thereafter more slowly with a half-life value of about 75 minutes. Approximately 75% of the administered dose is excreted in the urine during the first day after injection. The chief metabolite is R-(+)-1-(1-phenylethyl)-1H-imidazole-5-carboxylic acid, resulting from hydrolysis of etomidate, and accounts for about 80% of the urinary excretion. Limited pharmacokinetic data in patients with cirrhosis and esophageal varices suggest that the volume of distribution and elimination half-life of etomidate are approximately double that seen in healthy subjects.
(Reference: H. Van Beem, et.al., Anaesthesia 38 (Supp 38:61-62, July 1983).

Reduced plasma cortisol and aldosterone levels have been reported following induction doses of etomidate. These results persist for approximately 6 to 8 hours and appear to be unresponsive to ACTH stimulation. This probably represents blockage of 11 beta-hydroxylation within the adrenal cortex.
(References: 1. R.J. Fragen, et. al., Anesthesiology 61:652-656, 1984. 2. R.L. Wagner & P.F. White, Anesthesiology 61:647-651, 1984. 3. F.H. DeJong, et. al., Clin. Endocrinology and Metabolism 59:(6):1143-1147, 1984, and three additional drafts of Metabolic Studies, all submitted to NDA 18-228 on April 1, 1985).

INDICATIONS AND USAGE

Etomidate injection is indicated by intravenous injection for the induction of general anesthesia. When considering use of etomidate, the usefulness of its hemodynamic properties (see **CLINICAL PHARMACOLOGY**) should be weighed against the high frequency of transient skeletal muscle movements (see **ADVERSE REACTIONS**).

Intravenous etomidate is also indicated for the supplementation of subpotent anesthetic agents, such as nitrous oxide in oxygen, during maintenance of anesthesia for short operative procedures such as dilation and curettage or cervical conization.

CONTRAINDICATIONS

Etomidate is contraindicated in patients who have shown hypersensitivity to it.

WARNINGS

INTRAVENOUS ETOMIDATE SHOULD BE ADMINISTERED ONLY BY PERSONS TRAINED IN THE ADMINISTRATION OF GENERAL ANESTHETICS AND IN THE MANAGEMENT OF COMPLICATIONS ENCOUNTERED DURING THE CONDUCT OF GENERAL ANESTHESIA.

BECAUSE OF THE HAZARDS OF PROLONGED SUPPRESSION OF ENDOGENOUS CORTISOL AND ALDOSTERONE PRODUCTION, THIS FORMULATION IS NOT INTENDED FOR ADMINISTRATION BY PROLONGED INFUSION.

PRECAUTIONS

Do not administer unless solution is clear and container is undamaged. Discard unused portion (see **DOSAGE AND ADMINISTRATION**).

1. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No carcinogenesis or mutagenesis studies have been carried out on etomidate. The results of reproduction studies showed no impairment of fertility in male and female rats when etomidate was given prior to pregnancy at 0.31, 1.25 and 5 mg/kg (approximately 1X, 4X and 16X human dosage).

2. **Pediatric Use:** There are inadequate data to make dosage recommendations for induction of anesthesia in pediatric patients below the age of ten (10) years; therefore, such use in not recommended (see also **DOSAGE AND ADMINISTRATION**).

3. **Pregnancy Category C.** Etomidate has been shown to have an embryocidal effect in rats when given in doses 1 and 4 times the human dose. There are no adequate and well-controlled studies in pregnant women. Etomidate should be used during pregnancy only if the potential benefit justifies the potential risks to the fetus. Etomidate has **not** been shown to be teratogenic in animals. Reproduction studies with etomidate have been shown to:

    a. Decrease pup survival at 0.3 and 5 mg/kg in rats (approximately 1X and 16X human dosage) and at 1.5 and 4.5 mg/kg in rabbits (approximately 5X and 15X human dosage). No clear dose-related pattern was observed.

b. Increase slightly the number of stillborn fetuses in rats at 0.3 and 1.25 mg/kg (approximately 1X and 4X human dosage).

c. Cause maternal toxicity with deaths of 6/20 rats at 5 mg/kg (approximately 16X human dosage) and 6/20 rabbits at 4.5 mg/kg (approximately 15X human dosage).

4. **Labor and Delivery:** There are insufficient data to support use of intravenous etomidate in obstetrics, including Cesarean section deliveries. Therefore, such use is not recommended.

5. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when etomidate is administered to a nursing mother.

6. **Plasma Cortisol Levels:** Induction doses of etomidate have been associated with reduction in plasma cortisol and aldosterone concentrations (see **CLINICAL PHARMACOLOGY**). These have not been associated with changes in vital signs or evidence of increased mortality; however, where concern exists for patients undergoing severe stress, exogenous replacement should be considered.

ADVERSE REACTIONS

The most frequent adverse reactions associated with use of intravenous etomidate are transient venous pain on injection and transient skeletal muscle movements, including myoclonus:

1. Transient venous pain was observed immediately following intravenous injection of etomidate in about 20% of the patients, with considerable difference in the reported incidence (1.2% to 42%). This pain is usually described as mild to moderate in severity but it is occasionally judged disturbing. The observation of venous pain is not associated with a more than usual incidence of thrombosis or thrombophlebitis at the injection site. Pain also appears to be less frequently noted when larger, more proximal arm veins are employed and it appears to be more frequently noted when smaller, more distal, hand or wrist veins are employed.

2. Transient skeletal muscle movements were noted following use of intravenous etomidate in about 32% of the patients, with considerable difference in the reported incidence (22.7% to 63%). Most of these observations were judged mild to moderate in severity but some were judged disturbing. The incidence of disturbing movements was less when 0.1 mg of fentanyl was given immediately before induction. These movements have been classified as myoclonic in the majority of cases (74%), but averting movements (7%), tonic movements (10%), and eye movements (9%) have also been reported. No exact classification is available, but these movements may also be placed into three groups by location:

   a. Most movements are bilateral. The arms, legs, shoulders, neck, chest wall, trunk and all four extremities have been described in some cases, with one or more of these muscle groups predominating in each individual case. Results of electroencephalographic studies suggest that these muscle movements are a manifestation of disinhibition of cortical activity; cortical electroencephalograms, taken during periods when these muscle movements were observed, have failed to reveal seizure activity.

   b. Other movements are described as either unilateral or having a predominance of activity of one side over the other. These movements sometimes resemble a localized response to some stimuli, such as venous pain on injection, in the lightly anesthetized patient (averting movements). Any muscle group or groups may be involved, but a predominance of movement of the arm in which the intravenous infusion is started is frequently noted.

   c. Still other movements probably represent a mixture of the first two types.

Skeletal muscle movements appear to be more frequent in patients who also manifest venous pain on injection.

Other Adverse Observations

Respiratory System: Hyperventilation, hypoventilation, apnea of short duration (5 to 90 seconds with spontaneous recovery), laryngospasm, hiccup and snoring suggestive of partial upper airway obstruction have been observed in some patients. These conditions were managed by conventional countermeasures.

Circulatory System: Hypertension, hypotension, tachycardia, bradycardia and other arrhythmias have occasionally been observed during induction and maintenance of anesthesia. One case of severe hypotension and tachycardia, judged to be anaphylactoid in character, has been reported. (Reference: M. Sold and A. Rothhammer, Anaesthesist 34:208-210, 1985. Submitted to NDA 18-228 on 16 May 1985).

Gastrointestinal System: Postoperative nausea and/or vomiting following induction of anesthesia with etomidate is probably no more frequent than the general incidence. When etomidate was used for both induction and maintenance of anesthesia in short procedures such as dilation and curettage, or when insufficient analgesia was provided, the incidence of postoperative nausea and/or vomiting was higher than that noted in control patients who received thiopental.

OVERDOSAGE

Overdosage may occur from too rapid or repeated injections. Too rapid injection may be followed by a fall in blood pressure. No adverse cardiovascular or respiratory effects attributable to etomidate overdose have been reported.

In the event of suspected or apparent overdosage, the drug should be discontinued, a patent airway established (intubate, if necessary) or maintained and oxygen administered with assisted ventilation, if necessary.

The LD_{50} of etomidate administered intravenously to rats is 20.4 mg/kg.

DOSAGE AND ADMINISTRATION

Etomidate injection is intended for administration only by the intravenous route (see **CLINICAL PHARMACOLOGY**). The dose for induction of anesthesia in adult patients and in children above the age of ten (10) years will vary between 0.2 and 0.6 mg/kg of body weight, and it must be individualized in each case. The usual dose for induction in these patients 0.3 mg/kg, injected over a period of 30 to 60 seconds. There are inadequate data to make dosage recommendations for induction of anesthesia in patients below the age of ten (10) years; therefore, such use is not recommended.

Smaller increments of intravenous etomidate may be administered to adult patients during short operative procedures to supplement subpotent anesthetic agents, such as nitrous oxide. The dosage employed under these circumstances, although usually smaller than the original induction dose, must be individualized. There are insufficient data to support this use of etomidate for longer adult procedures or for any procedures in children; therefore, such use is not recommended. The use of intravenous fentanyl and other neuroactive drugs employed during the conduct of anesthesia may alter the etomidate dosage requirements. Consult the prescribing information for all other such drugs before using.

Premedication: Etomidate injection is compatible with commonly administered pre-anesthetic medications, which may be employed as indicated. See also **CLINICAL PHARMACOLOGY, ADVERSE REACTIONS,** and dosage recommendations for maintenance of anesthesia.

Etomidate hypnosis does not significantly alter the usual dosage requirements of neuromuscular blocking agents employed for endotracheal intubation or other purposes shortly after induction of anesthesia.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To prevent needle-stick injuries, needles should not be recapped, purposely bent, or broken by hand.

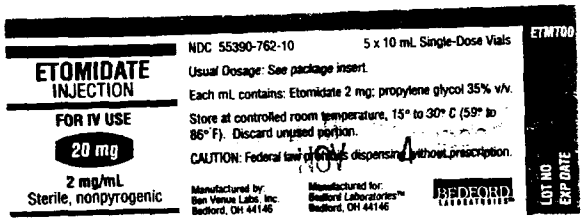
HOW SUPPLIED

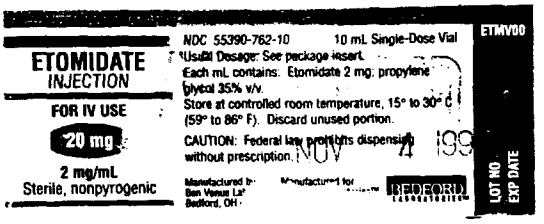
Etomidate Injection 2 mg/mL is supplied in 20 mg (10 mL single-dose vials) in trays of 5 - NDC 55390-601-10; and in 40 mg (20 mL single-dose vials) in trays of 5 - NDC 55390-602-20.
Store at controlled room temperature 15° to 30°C (59° to 86°F). Discard unused portion.
CAUTION: Federal law prohibits dispensing without prescription.

Manufactured for: Bedford Laboratories™, Bedford, OH 44146

Manufactured by: Ben Venue Laboratories, Inc., Bedford, OH 44146

December 1995 ETMP00


ETOMIDATE
INJECTION
FOR IV USE
20 mg
2 mg/mL
Sterile, nonpyrogenic
NDC 55390-762-10 5 x 10 mL Single-Dose Vials
Usual Dosage: See package insert.
Each mL contains: Etomidate 2 mg; propylene glycol 35% v/v.
Store at controlled room temperature, 15° to 30° C (59° to 86° F). Discard unused portion.
CAUTION: Federal law prohibits dispensing without prescription.
Manufactured by: Ben Venue Labs, Inc. Bedford, OH 44146
Manufactured for: Bedford Laboratories™ Bedford, OH 44146
BEDFORD LABORATORIES™
ETMT00
LOT NO
EXP DATE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NDC 55390-762-10 10 mL Single-Dose Vial
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BEDFORD LABORATORIES™
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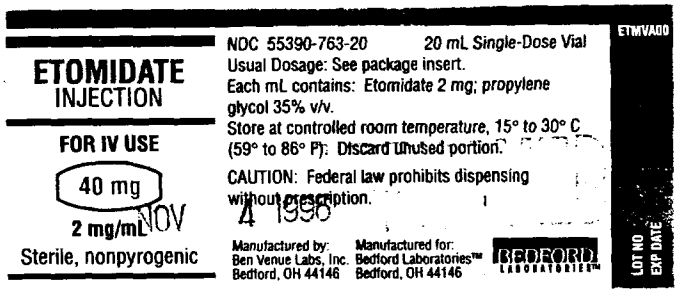
ETOMIDATE
INJECTION
FOR IV USE
40 mg
2 mg/mL
Sterile, nonpyrogenic
NDC 55390-763-20 20 mL Single-Dose Vial
Usual Dosage: See package insert.
Each mL contains: Etomidate 2 mg; propylene glycol 35% v/v.
Store at controlled room temperature, 15° to 30° C (59° to 86° F). Discard unused portion.
CAUTION: Federal law prohibits dispensing without prescription.
Manufactured by: Ben Venue Labs, Inc. Bedford, OH 44146
Manufactured for: Bedford Laboratories™ Bedford, OH 44146
BEDFORD LABORATORIES™
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LOT NO
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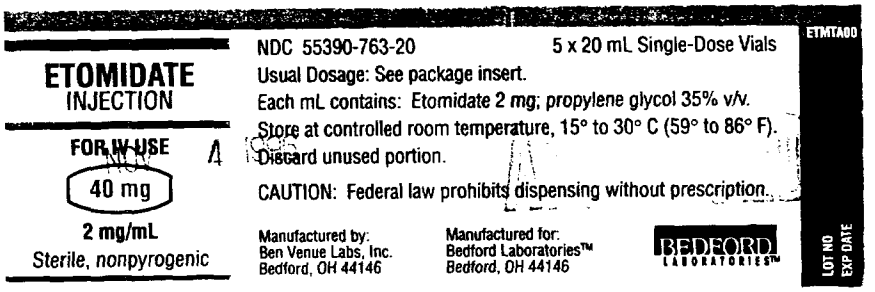
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Manufactured by: Ben Venue Labs, Inc. Bedford, OH 44146
Manufactured for: Bedford Laboratories™ Bedford, OH 44146
BEDFORD LABORATORIES™
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EXP DATE

AUG 1 1995

Etomidate Injection
2 mg/mL, 10 mL & 20 mL Vials
ANDA # 74-593
Reviewer: Man M. Kochhar
74593W.D94

Bedford Laboratories
Bedford, Ohio
Submission Date:
December 19, 1994

Review of a Waiver Request

The firm has requested a waiver of in vivo bioequivalence study for its sterile etomidate injections, 2 mg/mL in 10 mL and 20 mL vials based upon 21 CFR 320.22 (b)(1).

Comparative Formulation

Ingredients	Bedford mg/mL	Abbott mg/mL
Etomidate	2.0	2.0
Propylene Glycol Water for injection	qs to 1 mL	qs to 1 mL
Nitrogen	used as an inert atmosphere	used as an inert atmosphere

Deficiency: None

Comments:

1. The formulation of the test product (etomidate) and the innovator product (Amidate; Abbott) is similar in concentration of active and inactive ingredients.

2. The dosage form, route of administration (intravenous), strength (2 mg/mL), and labeling of the test product are identical to those of the innovator product, (Amidate). The dosage of test and reference product are same.

3. From the bioequivalence point of view, the waiver of in vivo bioequivalence study requirement should be granted based on 21 CFR 320.22 (b)(1). The batch size was

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Bedford Laboratories on its sterile Etomidate 2mg/mL injections in 10 mL and 20 mL vials fall under 21 CFR 320.22 (b)(1) of the Bioavailability/Bioequivalence regulations. The waiver of in vivo bioequivalence study for Etomidate (test product) 2 mg/ml injection in 10 mL and 20 mL vials is granted.

From the bioequivalence point of view, the Division of Bioequivalence deems the test injection of Etomidate 2 mg/mL in 10 mL and 20 mL vials to be bioequivalent to Amidate 2 mg/mL in 10 ml and 20 mL ampules, manufactured by Abbott Laboratories.

The firm should be informed of the recommendation.

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalece

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Ramaprasad M. Mhatre Date: 6/14/95

Concur: 6/1/95
Keith K. Chan, Ph.D
Director
Division of Bioequivalence

MMKochhar/mmk/5-22-95; 74-593

cc: ANDA # 74-593 original, HFD-600 (Hare), HFD-630, HFD-658 (Mhare, Kochhar), Drug File, Division File.